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(54) Rapidly-dispersable compositions containing polydextrose.

(57) Novel pharmaceutical and/or cosmetic compositions are disclosed containing a matrix prepared by melt-spinning polydextrose with one or more medicaments and/or cosmetic ingredients. Methods of preparing such compositions as well as treating various maladies are also disclosed.

EP 0 570 327 A1

BACKGROUND OF THE INVENTION

The present invention relates to novel polydextrose-containing materials and to methods for preparing the same. In particular, the invention relates to readily dispersable polydextrose-containing medicaments or cosmetics.

In commonly-assigned U.S. Patent Nos. 4,855,326 and 4,873,085, various active agents having pharmacological and/or cosmetic properties were combined with readily water-soluble melt-spinnable materials such as sugars or cellulosic substances. The active agents spun with these materials demonstrate enhanced solubility.

Commonly-assigned U.S. Patent Nos. 5,011,532 and 5,096,492 contain examples of oleaginous substances that are mixed with sugar and melt-spun. The spun products disperse readily in water, forming colloidal or pseudo-colloidal dispersions. The '532 patent explains how oleaginous substances such as vegetable oil, mineral oil, baby oil, margarine, lanolin, cocoa butter and the like, which characteristically have little or no affinity for water, can have this characteristic altered by mixing the oleaginous substance with sugar and melt-spinning the mixture in a cotton candy spinning machine or equivalent. The disclosure of the '532 patent is incorporated herein by reference.

Other disclosures dealing with spinning substances with one or more sugars will be found in commonly-assigned U.S. Patent Nos. 4,873,085; 4,997,856; 5,028,632 and 5,034,421. Generally, each of these disclosures are directed to melt-spinning sugar by introducing sugar and various ingredients into a cotton candy spinning machine. Such equipment is normally operated at a temperature of around 200°C and at speeds of about 3,500 r.p.m. Melt-spinning in such equipment relies upon certain characteristics of sucrose, such as high crystallinity and high physical and chemical lability. The spun products disclosed in these patents are described as taking the form of a floss or mass of spun fibers.

Although the products discussed above are rapidly dispersable and even compactable, it has been desired to provide spun products in alternative forms which would facilitate handling of the spun product. In particular, it has been desired to provide the spun products in a form which is easier to work with, pour, and mix with other solids, etc. Such alternatives would provide higher efficiency for subsequent processing when the matrix is included in various goods or finished products.

Some efforts to alter the morphology of melt-spun products have centered around finding alternatives for sucrose. Attempts to spin non-sucrose or low-sucrose-containing saccharides have been, for the most part, unsuccessful. Feedstock having little or no sucrose as a carrier component were found to char during melt-spinning and were generally non-processable, especially on a commercial scale. It has been the belief of the artisan that sucrose is an important ingredient in feedstocks for melt-spinning processes.

Polydextrose is a non-sucrose, essentially non-nutritive carbohydrate substitute. Polydextrose can be prepared through polymerization of glucose in the presence of polycarboxylic acid catalysts and polyols. Generally, polydextrose is known to be commercially available in three forms: polydextrose A and polydextrose K, which are powdered solids, and polydextrose N supplied as a 70% solution. Each of these products also contain some low molecular weight components, such as glucose, sorbitol and certain oligomers.

In the past, most of the interest in polydextrose has centered around its use in various edible compositions. For example, polydextrose has stimulated interest in the food arts as a low-calorie bulking agent or as a part of many low-calorie or light foods since it has only about one-quarter of the calories of sucrose. Non-food related uses for the material have largely been ignored.

Unfortunately, the ability to disperse polydextrose and use it in different products has been limited by certain physical and chemical phenomena. Unlike most saccharide products, it is relatively unreactive and physically resistive to mixing and dispersing. While artisans have been able to process sugar to enhance its utility in food and other products, polydextrose heretofore did not appear to be as versatile.

The technical and processing difficulties alluded to above have therefore hampered the artisan's use of polydextrose and polydextrose-containing materials. If these difficulties could be overcome, especially in the areas of dipersability and solubility, the artisan would gain a useful non-sucrose alternative.

It is therefore an object of the invention to provide polydextrose-containing products having improved dispersability in liquids.

Other and further objects of the present invention are set forth in the following description, and its scope will be pointed out in the appended claims.

SUMMARY OF THE INVENTION

The present invention includes polydextrose-containing products prepared by melt-spinning a polydextrose feedstock containing one or more adjunct materials such as medicaments and/or cosmetics to provide a matrix.

The polydextrose matrices of this invention are readily dispersable in solids and liquids. Readily dispersable means that the polydextrose matrix can be mixed with reduced mechanical mixing force when compared to polydextrose-containing feedstock which has not been melt-spun.

Numerous materials can be melt-spun with polydextrose conferring improved dispersion and solubility properties on the total product. These products have a wide variety of uses including pharmaceutical products, cosmetics and a variety of other products.

The present invention also includes novel processes for preparing a wide variety of melt-spun polydextrose-containing products. The products are prepared by admixing polydextrose and adjuvant materials to form a feedstock, melt-spinning the feedstock and recovering the product. Further processes include incorporating the melt-spun matrix with additional ingredients to produce pharmaceuticals, medicaments, cosmetics or the like. Moreover, methods of treatment are also included wherein the matrix is affixed to a site of treatment.

As a result of the present invention, a useful non-sucrose-containing matrix is provided. This alternative form allows bulking and dispersing properties beyond what sucrose-based matrices alone, usually in the form of floss and/or fibers, could provide. Thus, the versatile matrix can be readily used alone or in combination with other ingredients to form cosmetic or medicinal preparations, or, in other aspects, easily included as part of a topical lotion, ingestible liquid, tablet, capsule or the like.

The applications for these polydextrose-containing materials are vast. Consequently, pharmaceutical and cosmetic artisans have been equipped with a new tool which can be used to significantly enhance medicinal, cosmetic or even industrial systems especially when enhanced dispersability of a particular material in a useable medium is needed.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is a composition and method utilizing polydextrose and one or more adjuvant materials to provide novel products. In particular, melt-spinning allows alteration of various physical, and in some cases, apparent chemical properties. Thus, polydextrose and products containing it can be altered with respect to solubility, wetability, and/or dispersability in aqueous and non-aqueous media. Moreover, the hydrophobic and/or lipophobic characteristics of polydextrose can be modified to provide the new products described herein, such as medicaments and/or cosmetics. In some aspects, the products of this invention can be used in lieu of freeze-dried materials.

The solid forms of polydextrose are in a form which is somewhat like powdered milk. As such, it can be difficult to disperse or dissolve. Vigorous stirring is required to incorporate it into water or aqueous liquids and it can lump or form difficult-to-disperse clumps of material, i.e., the "fish-eye" phenomenon. In contrast thereto, the melt-spun polydextrose-containing products of the present invention enter into a dispersion in aqueous liquids with little or no mechanical agitation. Thus, the melt-spun polydextrose of the invention overcomes certain processing difficulties such as clumping and inability to flow in a dry state. Further, the novel polydextrose-containing compositions of this invention, in addition to enhanced dispersion properties, can be used to hold one or more ingredients combined in the matrix and release it over time.

As noted above, the products of this invention are prepared by a melt-spinning operation. One of the preferred methods for melt-spinning is through the use of apparatus such as those adapted to the production of cotton candy, or floss, from sugar. Illustrative of such machines is the Econo Floss Machine Model 3017 manufactured by Gold Medal Products Company of Cincinnati, Ohio. It will be appreciated by those skilled in the art from the present description that any apparatus or physical process which provides similar shear forces and time/temperature gradient conditions can also be used. For simplicity in disclosing and describing this invention, the term "melt-spinning" will be understood to mean a flash flow process which includes a combination of temperature, shear, flow, flow rate, mechanical forces and thermal gradients of the type used in a cotton candy-type machine. The apparatus is operated at a temperature and speed which permits flash flow but does not deteriorate the material undergoing the processing.

The flash flow process (or conditions comparable thereto) provides sufficient internal flow to permit transition in structure of the carrier material, herein polydextrose, without degradation of the carrier or any adjuvant material. Internal flow occurs when the infrastructure of the material breaks down sufficiently to permit movement of material at a subparticle level, and probably at a molecular level. At a molecular level, internal flow contemplates the movement of molecules relative to each other.

Internal flow of material is generally associated with the melting point or glass transition point. In this situation, however, it is contemplated that the combined application of heat and external force is sufficient to produce the flow at temperatures below the melting or glass transition point for most compositions.

An important benefit obtained by including polydextrose in the inventive matrix is that mixtures containing polydextrose can be spun at temperatures well below that of many other materials. For example, polydextrose

has been successfully spun at temperatures of about 140°C, compared to temperatures of around 200°C for sucrose. Polydextrose, therefore, provides the additional benefit of allowing lower processing temperatures in addition to short dwell times to allow a matrix to be formed before any degradation occurs.

An additional benefit associated with including polydextrose is that the resulting matrix can be in the form of a particle, flake, spicule or the like, conferring substantial advantages over sucrose-based forms such as a floss or spun fibers. These alternative morphologies allow subsequent processing and mixing to be more readily undertaken.

In one aspect of the invention, the adjuvant materials included with the polydextrose are medicament-related materials. Suitable categories of such ingredients may vary widely. Illustrative categories and specific examples include:

(a) Antitussives, such as dextromethorphan, and chlorphedianol hydrochloride;
(b) Antihistamines, such as chlorpheniramine maleate and terfenadine;
(c) Decongestants, such as phenylephrine, phenylpropanolamine, pseudoephedrine and ephedrine;
(d) Various alkaloids, such as codeine and morphine;
(e) Mineral supplements such as potassium chloride;
(f) Laxative, vitamins and antacids;
(g) Ion-exchange resins such as cholestyramine;
(h) Anti-cholesterolemic and anti-lipid agents;
(i) Antiarrhythmics such as N-acetyl-procainamide;
(j) Antipyretics and analgesics such as acetominophen, aspirin and ibuprofen;
(k) Appetite suppressants such as phenylpropanolamine hydrochloride or caffeine;
(l) Expectorants such as guaifenesin;
(m) Anti-anxiety agents such as diazepam; and
(n) Anti-ulcer agents such as sucralfate.

A non-limiting list of other active ingredients includes anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, antimanics, stimulants, gastrointestinal agents, sedatives, antidiarrheal preparations, anti-anginal drugs, vasodialators, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, antipsychotics, antitumor drugs, anticoagulants, antithrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and antithyroid preparations, diuretics antispasmodics, uterine relaxants, mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, cough suppressants, mucolytics, anti-uricemic drugs, and mixtures thereof.

The medicaments contemplated herein are particularly well-suited for use when it is desired to disperse the agent in aqueous liquids and/or mask cover the undesirable tastes of actives. Generally, the medicament is mixed with polydextrose and melt-spun to obtain the medicament product. The flavor of unpleasant medicaments can also be masked or altered if desired by adding a flavoring agent and/or a sweetening agent to the pre-spun mixture.

In an alternative aspect of the invention, the adjuvant materials included with the polydextrose are cosmetic-related ingredients. Cosmetic ingredients are those materials which have a skin beautifying and/or complexion-related activity. Such products can be used externally on hair, skin or both. A non-limiting list of ingredients which have appearance-improving cosmetic activity includes dimethyl siloxanes, mucopolysaccharides, methyl and propyl parabens, biotin, lanolin, aloe, glycerin, mineral oil, nicotinamide compounds, sun screens, such as para-aminobenzoic acid, hair conditioners, moisturizers, moisturizing creams, astringents, powders such as talcs and combinations thereof.

In each of the above melt-spun aspects, the medicament or cosmetic ingredients can be included (1) within the matrix, (2) in addition to the matrix, or (3) both inside and outside the matrix.

It will be understood by those skilled in the art from the present description that additional materials can be included with the polydextrose and principle active ingredients. Thus, colors, dyes, pigments, antioxidants, preservatives and similar ingredients can be added in both the matrix and product in which the matrix is included. Such materials serve to improve the appearance, aroma, shelf-life or other properties of the products prepared and described herein. Moreover, the final products can also contain those adjuvant materials which are particularly suited for particular end uses.

The nature and amount of all materials included in the matrix will vary greatly. For example, it should be understood that polydextrose is spinnable by itself. Therefore, in general, the limit of polydextrose that can be included in any given composition has more to do with the desired morphology and nature of host matrix-carrier and guest activity. The amount of active material included in the matrix and/or product containing the matrix will depend upon the active and the amount required to achieve a desired therapeutic cosmetic effect. The exact amounts of the materials which make up the matrix and final products in which the matrix is included

will therefore be within the level of ordinary skill of those in the art.

In further aspects of the invention, supplemental materials such as bioadhesives, dispersants, surfactants and the like can be included in the matrix, products containing the matrix, or both. For example, bioadhesive-type materials such as hydrogels or synthetic materials such as polyvinyl-pyrrolidone are useful. Dispersants such as polyacrylates and alginates are also useful.

A non-limiting list of surfactants which are useful in combination with the matrix of the invention include as follows: anionic surfactants such as alkyl carboxylates, alkyl sulfates, ethoxylated alkyl sulfates, sulfosuccinate esters, isothionates, sarcosinates, sodium lauryl sulfoacetates, fatty acid-polypeptide condensates, linear alkyl arylsulfonates (LAS), alpha-olefin sulfonates (AOS), organic phosphate esters; cationic surfactants such as sodium lauryl sulfate (SLS), cetrimonium bromide and polysorbates; amphoteric surfactants such as alkylamino propionates, acyl ethylenediamines and betaines; non-ionic surfactants such as ethoxylated and propoxylated derivatives and polyol esters including sorbitan esters, polyoxyethylene ethers; alkyl polyglycosides, sulfonic acid/linear alkylate sulfonates, silicon derived phosphate esters, non-oxynol surfactans, Triton™ surfactants and alkylphenols.

The invention also includes methods of treatment. The methods include contacting affected areas with the spun matrices containing medicaments such as described herein. The medicament-containing matrix can be placed in contact with the affected area in the as-spun form, as a compacted wafer or after being dispersed in a liquid. In the situations where the matrix is affixed directly to an affected area, non-exacerbating bioadhesive-type materials can also be included.

It will be understood from the present description that the dosages of any medicaments described herein can be varied depending upon the requirements of the patient, the severity of the condition being treated and similar considerations. The actual optimum dosage is within the skill of the artisan.

EXAMPLES

The following examples serve to provide further appreciation of the invention but are not meant in any way to restrict effective scope of the invention. Unless indicated otherwise, the Econo Floss machine referred to above was used to form the spun matrix. Operating temperatures were approximately 140°C - 150°C, spinning speed was approximately 3,500 r.p.m.

EXAMPLE 1

ACETOMINOPHEN-POLYDEXTROSE MATRIX	
INGREDIENTS	**WEIGHT (GRAMS)**
Acetominophen	20
Polydextrose K	80
Vegetable Oil	40

In this Example, an acetominophen-containing matrix is prepared. All of the ingredients are thoroughly mixed and spun. A white spicule-like flake was obtained.

A tablespoon of the resulting flakes was contacted with water at room temperature. After quickly dissolving, a colloidal suspension was formed which had a viscosity thicker than that of the water alone.

A similar quantity of acetominophen, polydextrose and vegetable oil mixed together, but in non-spun condition, was placed in a container of water. The ingredients failed to disperse, leaving oil patches and clumps of dry materials.

EXAMPLES 2 - 3

The examples set forth below further exemplify the present invention.

INGREDIENTS	WEIGHT (PERCENT)	
	EX. 2	EX. 3
Acetominophen	60.0	80.0
Polydextrose	30.0	15.0
Corn Oil	10.0	5.0
	100.0	100.0

In Examples 2 and 3, acetominophen melt-spun matrices were prepared. In each case, in spite of the low amount of polydextrose, the mixtures were melt-spun and provided light airy flakes. In each case, the flakes dispersed readily in water. The corn oil, even in amounts as low as 5%, was found to reduce the dust blow-up which otherwise occurs during spinning. It should be noted, however, that the presence of a vegetable oil is not necessary and that the ingredients could be spun as dry powders.

EXAMPLE 4

ANTI-ULCER COMPOSITION	
INGREDIENTS	WT. (GRAMS)
Sucralfate (Powder)	50.0
Xanthan Gum	10.0
Corn Oil	25
Peppermint Oil	2
Polydextrose-K	438

In this Example, a sucralfate-containing anti-ulcer composition was prepared. Initially, the carrier material was prepared by mixing the xanthan gum, sucralfate, and polydextrose until a substantially homogeneous mixture was obtained. Thereafter, the corn oil and peppermint oil flavorant were added while mixing was continued. The resultant mixture was then spun at about 140°C at 3600 r.p.m. A white spicule-like flake was obtained.

A one tablespoon quantity of the resulting matrix was added to a glass of tap water at room temperature. After quickly dissolving, a creamy yellow colloidal suspension was formed.

The resultant mixture was ingested by a host having distress from an ulcerated stomach. The inventive composition provided dramatic relief of stomach ulcer pain instantaneously. It appears that the unique combination of ingredients subjected to the high shear and heat processing had a remarkable effect on the speed and the extent of the treatment.

EXAMPLE 5

ANTI-ULCER COMPOSITION	
INGREDIENTS	WT. (GRAMS)
Sucralfate (Powder	50
Xanthan Gum	10
Corn Oil	25
Peppermint Oil	2
Polydextrose-K	438

In this Example, the medicament-containing matrix is prepared as in the Example 4. Fifteen grams of the flakes are added to a small amount of water to produce a viscous dispersion.

The dispersion was then placed on ulcer-bearing oral cavity tissue of an affected host. The hydrogel portion of the composition, xanthan gum, along with the medicament remain affixed to the oral cavity ulcer-bearing tissue to provide instantaneous relief from the discomfort associated with the ulcerated tissue in the oral cavity.

EXAMPLE 6

INGREDIENTS	WT. (GRAMS)
Cocoa Butter	16 gr.
Samarkand Fragance Oil	16 gr.
Gleason Lite Mineral Oil	16 gr.
Polydextrose-K	160 gr.
Ethanol 95%	3 gr.

The ingredients were mixed together with a glass rod for about 10 minutes. This mixture was spun at about 140°C at 3600 r.p.m. producing tan chips.

The tan chips were dissolved rapidly in tepid water producing a gorgeous colloidal bath water which is very comforting to the skin.

EXAMPLE 7

INGREDIENTS	WT. (GRAMS)
Dimethyl Polysiloxane	10 gr.
Polydextrose-K	90 gr.

In this Example, the above ingredients were mixed by hand and then in a Cuisinart for four minutes. The mixture was spun at 140°C at 3600 r.p.m. producing long silky chips.

The chips are then put in hot water resulting in a strong colloidal dispersion. The colloidal dispersion can be used in cosmetics to provide improved contact and adherence to the skin. Dimethyl Polysiloxane is a desired ingredient in many cosmetic and hair conditioner formulations but it is very difficult to form colloidal dispersions by conventional techniques.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to claim all such changes and modifications as fall within the true scope of the invention.

Claims

1. A pharmaceutical composition comprising a polydaxtrase-based matrix resulting from melt-spinning a medicament with polydextrose.

2. A method of preparing a pharmaceutical composition comprising providing a matrix prepared by melt-spinning polydextrose and a medicament.

3. The invention of Claims 1 or 2, wherein said medicament melt-spun with said polydextrose is selected from substances such as antitussives, antihistamines, decongestants, alkaloids, mineral supplements, laxatives, vitamins, antacids, ion exchange resins, anti-cholesterolemics, anti-lipid agents, antiarrhythmics, antipyretics, analgesics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psycho-tropics, antimanics, stimulants, gastrointestinal agents, sedatives, antidiarrheal prep-

arations, anti-anginal drugs, vasodialators, anti-hypertensive drugs, visoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, antitumor drugs, anticoagulants, antithrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, cough suppressants, mucolytics, anti-uricemic drugs, or the like and mixtures thereof.

4. The pharmaceutical composition of Claim 1, further comprising an additional medicament.

5. The method of Claim 2, further comprising combining an additional medicament with said matrix.

6. The invention of claims 4 or 5, wherein said additional medicament is selected from substances such as antitussives, antihistamines, decongestants, alkaloids, mineral supplements, laxatives, vitamins, antacids, ion exchange resins, anti-cholesterolemics, anti-lipid agents, antiarrhythmics, antipyretics, analgesics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, anti-infectives, psychotropics, antimanics, stimulants, gastrointestinal agents, sedatives, antidiarrheal preparations, anti-anginal drugs, vasodialators, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, antipsychotics, antitumor drugs, anticoagulants, antithrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper- and hypoglycemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, mineral and nutritional additives, antiobesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, cough suppressants, mucolytics, anti-uricemic drugs, or the like and mixtures thereof.

7. The pharmaceutical composition of Claim 1, wherein said matrix further comprises an oleaginous substance.

8. The method of Claim 2, wherein said matrix further comprises an oleaginous substance.

9. The pharmaceutical composition of Claim 7, wherein said oleaginous substance is selected from substances such as vegetable oils, corn oil, sunflower oil, olive oil, canola oil, or the like and mixtures thereof.

10. The pharmaceutical composition of Claim 7, wherein said oleaginous substance is present in an amount of from about 2% to about 20% by weight of said matrix, preferably in an amount of from about 5% to about 15% by weight of said matrix.

11. The pharmaceutical composition of Claim 1, wherein said matrix further comprises a member of the group of substances such as surfactants, dispersing aids, adhesion promoters, flavors, sweeteners, dyes, preservatives, or the like and mixtures thereof.

12. The pharmaceutical composition of Claim 11, wherein said surfactants are selected from substances such as anionic surfactants, cationic surfactants, nonionic surfactants, amphoteric surfactants, alkyl polyglycerides, sulfonic acid/linear alkylate sulfonates, silicon derived phosphate esters, non-oxynol surfactants, Triton™ surfactants, alkylphenols, or the like and mixtures thereof;

optionally said dispersing aids are selected from substances such as polyacrylates, alginates, or the like and mixtures thereof;

optionally said adhesion promoters are selected from substances such as polyvinylpyrrolidone and hydrogels; and

optionally said hydrogels are selected from substances such as xanthan gum, guar gum, carrageenan gum, gum tragacanth, alginates such as sodium alginate, gum karaya, locust bean gum, gum acacia, or the like and mixtures thereof.

13. The pharmaceutical composition of Claim 1, further comprising a member of the group of substances such as surfactants, dispersing aids, adhesion promoters, flavors, sweeteners, preservatives, dyes, or the like and mixtures thereof.

14. The method of Claim 2, further comprising combining a member of the group of substances such as surfactants, dispersing aids, adhesion promoters, flavors, dyes, sweeteners, preservatives, or the like and mixtures thereof with one of said matrix, said composition or said matrix and said composition.

15. A cosmetic composition comprising a polydextrose-based matrix resulting from melt-spinning a cosmetic ingredient with polydextrose.

16. A method of preparing a cosmetic composition comprising providing a matrix prepared by melt-spinning polydextrose and a cosmetic ingredient.

17. The invention of Claims 15 or 16, wherein said cosmetic ingredient is selected from substances such as dimethyl siloxanes, mucopolysaccharides, methyl and propyl parabens, biotin, lanolin, aloe, glycerin, mineral oil, nicotinamide compounds, sun screens, hair conditioners, moisturizers, moisturizing creams, astringents, powders, or the like and mixtures thereof.

18. The invention of Claims 15 or 16, further comprising an additional cosmetic ingredient.

19. The cosmetic composition of Claim 18, wherein said additional cosmetic ingredient is selected from substances such as dimethyl siloxanes, mucopolysaccharides, methyl and propyl parabens, biotin, lanolin, aloe, glycerin, mineral oil, nicotinamide compounds, sun screens, hair conditioners, moisturizers, moisturizing creams, astringents, powders, or the like and mixtures thereof.

20. The invention of Claims 15 or 16, wherein said matrix further comprises an oleaginous substance.

21. The invention of Claim 20, wherein said oleaginous substance is selected from substances such as vegetable oils, corn oil, sunflower oil, olive oil, canola oil, or the like and mixtures thereof.

22. The cosmetic composition of Claim 15, wherein said matrix further comprises a member of the group of substances such as surfactants, dispersing aids, adhesion promoters, flavors, sweeteners, dyes, preservatives, or the like and mixtures thereof.

23. The method of Claim 16, further comprising combining a member of the group of substances such as surfactants, dispersing aids, adhesion promoters, flavors, dyes, sweeteners, preservatives, or the like and mixtures thereof with one of said matrix, said composition or said matrix and said composition.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 65 0019

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
E	WO-A-9 311 750 (FUISZ TECHNOLOGIES LTD) * the whole document * * claim 7 *	1-14	A61K9/70 A61K7/00
E	WO-A-9 308 699 (FUISZ TECHNOLOGIES LTD) * page 9, line 11 - page 10, line 6 * * page 26; example 3 * * page 30 - page 31; example 13 *	15-23	
Y D	WO-A-8 808 298 (FUISZ) * the whole document * & US-A-4 855 326	1-6	
Y D	WO-A-9 107 952 (FUISZ PHARMACEUTICAL LTD.) * the whole document * & US-A-4 997 856	7-14	
Y D	WO-A-8 808 296 (FUISZ) & US-A-4 855 326 * the whole document *	15-23	
Y	PATENT ABSTRACTS OF JAPAN 21 November 1990 & JP-A-22 21 232 (WAKOUDOU KK) 4 September 1990 * abstract *	1-23	TECHNICAL FIELDS SEARCHED (Int. Cl.5) A61K
Y	DATABASE WPI Derwent Publications Ltd., London, GB; AN 91-047889 & JP-A-2 312 582 (JINNAN SHUZO KK) 27 December 1990 * abstract *	1-23	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	24 AUGUST 1993	BENZ K.F.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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(56) Documents cited
GB A 2075818 GB 0543309 WO A1 8300284
GB 0931149 GB 0490001 US 4271142

(58) Field of search
A5B

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(54) Encapsulated medicament in sweet matrix

(57) An orally administrable medicament is prepared into a dosage form which eliminates the unpleasant taste and mouth feel of the medicament and is easily and pleasantly ingested even by children, by microencapsulating the medicament and embedding the microcapsules into a soft, sweet palatable matrix, such as chocolate.

GB 2 147 501 A

SPECIFICATION

Microencapsulated medicament in sweet matrix

Field of the Invention

The present invention relates to a manner in which medicaments may be orally administered to children or others in a pleasant manner in which the taste of the medicament is totally hidden. More particularly, the present invention relates to a medicament form for permitting such administration.

Background of the Invention

Oral medication is one of the most popular methods of drug administration into the body because it enables self-medication of the patient. In this category, palatability is an extremely important factor in formulating pharmaceutical forms. Because of the strong upleasant taste of many medicaments the value of many drugs is substantially diminished. This is particularly common among children's medications, but is also true for adults. In order to overcome these problems of unpleasant taste and unpalatable taste, many flavorings have been employed with pharmaceuticals. Thus, it is very common to administer many children's drugs as flavored syrup. Unfortunately, flavoring merely masks the unpleasant mouth taste but affects the palatability only slightly. A number of medications have an especially bitter taste, and even adults reluctantly take them. In many such cases even syrups cannot mask the bitter taste, thus constituting a difficult pharamaceutical problem.

Among the flavorings which have been used for the purpose of masking is chocolate. Examples of patents in which chocolate is used in conjunction with medicaments, are U.S. patents 4,271,142 and 4,327,077 to Puglia et al, U.S. patent 3,697,641 to Ahrens, U.S. patent 199,139 to Clark, British patent 543,309 to Evans and Australian patent 7310/32 to Jones et al. Children's vitamins encased in chocolate are also known and on the market, but in these products same of the vitamins are not sufficiently stable. Laxatives in chocolate are also well known. In all of these, however, the unpleasant taste is merely masked and the medicines still adversely affect the flavor of the chocolate and the palatability of the medicine is not substantially improved. Furthermore, stability problems caused by direct contact of the drug with the chocolate can arise.

In order to permit the release of orally administered drugs within selected portions of the alimentary canal, i.e. the stomach or intestine, pills in which the medicaments are protected with the desired coating have been developed. A more advanced pharmaceutical form for this purpose is the microencapsulated drug where one tablet (or large capsule) contains a few hundred tiny (approximately 0.5–0.8mm) capsules (called microcapsules) constaining the drug. The type of coating encapsulating the drug is chosen according to the medication desired and the desired release characteristics.

Summary of the Invention

It is an object of the present invention to provide a new form of medication for oral administration.

It is another object of the present invention to provide a new form of medicament for oral administration in which the unpalatable taste and mouth feel of the medicament is totally eliminated.

It is further object of the present invention to provide a new form of medicament which is very palatable to children, as well as to adults.

It is yet another object of the present invention to provide a method for administering medicaments for children in a manner which will be palatable to the child.

These and other objects are obtained in accordance with the present invention by micoencapsulating the drug to be administered and embedding the microcapsules in a soft sweet palatable matrix such as chocolate. The combination of encapsulation of the drug and the use of the soft sweet matrix, such as chocolate, achieves the goals of both preventing the unpleasant taste which the drugs may possess and overcoming the palatability problem that may arise when one tries to ingest the drug itself. The encapsulation will prevent the unpleasant taste which many drugs possess and the chocolate matrix will serve as a way to overcome the palatibility problem. Furthermore, the encapsulation will avoid the medication giving an off-flavor to the chocolate itself, which inevitably occurs when drugs are mixed directly with a chocolate matrix without first being microencapsulated and will avoid loss of stability of the medicament by eliminating direct contact of the medicament with the chocolate.

This combination will totally eliminate the unpleasant taste of the medicines and the patient will only taste the chocolate or other soft sweet matrix. Obviously, this system is superior to any other existing method.

Detailed Description of Preferred Embodiments

As the soft sweet matrix in accordance with the present invention, there may be used any palatable foodstuff which can be masticated without substantial chewing and easily swallowed, preferably a confection which is sweet to the taste and will be readily accepted by the child or adult. While chocolate is the preferred matrix, it should be understood that other soft sweet matrices such as fudge, marshmallows, peanut butter, carob, solid yogurt, or even cookies of appropriate consistency may be used as the matrix, alone or in combination with other matrices. The matrix cannot be hard, such as a hard candy, because the heavy pressure which would be involved in chewing such a matrix would break the microcapsules and thus destroy the purpose of the present invention. A soft chocolate, such as sweet or milk chocolate, is ideal for this purpose as substantial chewing is not required for complete mastication and the chocolate and embedded microcapsules can be masticated and swallowed without breaking the microcapsules.

The microcapsules should be of small size in order to ensure easy and pleasant palatability. Thus, the size should be less than 2mm diameter, preferably less than 1mm in diameter, and most preferably in the range of 10–100 microns. The smaller the microcapsules, the less likely they are to be noticed by the patient, and the more likely that the capsules will escape chewing and essentially will be swallowed intact.

A very wide range of medicaments are suitable for inclusion in the microcapsules used in the present invention. Such medicaments include antibiotics and other antibacterial agents, analgesics, antihistamines, decongestants, anti-inflammatory agents anti-hypertensive agents, hypnotics, sedatives, tranquilizers, alkaloids, diuretics, vasodilators, hormones, vitamins or any other medicament frequently used in oral dosage form. Those with especially bitter taste, such as penicillin, are, of course, particularly suited for use in the present invention.

Suitable antibiotics include penicillins, cephalosporins, tetracyclines, chloramphenicol, streptomycins, and macrolids. Suitably fully synthetic anti-bacterial agents include nitrofurantoin and the sulphonimides. Suitable anti-inflammatory or analgesic agents include aspirin and acetaminophen. Suitable pyschotropic medicaments include -methyldopa and guanethidine. Suitable diuretics include aminophyline and acetazolamide.

Antibacterials include benzylpenicillin, phenoxymethylpenicillin, ampicillin and its pivaloyloxymethyl or phthalyl esters, amoxycillin, cloxicillin, dicloxicillin, flucloxicillin, carbenicillin, propicillin, methicillin, cephalexin, cephaloridine, cephaloglycine, cephalothin, tetracycline, oxytetracycline, chlorotetracycline, novobiocin, neomycin, chloramphenicol, sulphathiazole, succinyl sulphathiazole, sulphadimidine, streptamycin, erythromycin, fusidic acid, griseofulvin, kanamycin, lincomycin, spiramycin, sulphamethoxy pyrideazine, sulphaphenazole, salicylazosulphapyridine, sulphamethoxazole and trimethoprin.

Suitable vitamins or nutritional supplements include thiamine, nicotinamide, ascorbic acid, pyridoxine, riboflavine, tryptophan, pantothenates, glycerophosphates and mixtures of these and other vitamins.

Other medicaments include alcofenac, theophylline, hexobendine, xylamide, and 0-(4-methoxyphenylcarbomoyl)-3-diethylaminopropiophenone oxime.

Normally any of the medicaments to be microencapsulated may be used as their conventional salts, hydrates or the like.

This list is not intended to be all inclusive as any medicament which can be microencapsulated may be administered in the form of the present invention.

A broad range of encapsulating agents and methods of encapsulation may also be used in the present invention. The only limitations on the encapsulation material are that it must be such that the active core material will not come into contact with the chocolate, or other matrix, during production or storage, it must be non-toxic and harmless, it must allow the core material to become released in the stomach or gastro-intestinal tract and it must be compatible with the sweet matrix. Any capsule materal known to the art may be used in the present invention and any method of microencapsulation may be used. See, for example, the methods of microencapsulation discussed in Sparks, R.E., "Microencapsulation", *Kirk-Othmer Encyclopedia of Chemical Technology*, third edition, volume 15 (1981), pages 470–493. As is well known, the microencapsulation material may be chosen for sustained release properties or for release in a preferred area of the alimentary canal (e.g., stomach or intestine). It is preferred that a method be used such that as high a weight percent as possible of the microcapsules be active material. For example, U.S. patent 4,016,254 teaches a method of microencapsulation in which the microcapsules have an average diameter of from 100μ to 300μ and which comprise 94% to 99.9% of a medicament coated by 0.1% to 6% of a coating agent. See also U.S. patent 3,119,742. Any such microencapsulation procedure known to the art or discovered by the art in the future may be used to make the encapsulated medicament for use in the present invention. The present invention does not relate to techniques of microencapsulation per se, but only to the use of microcapsules of medicaments in a soft sweet matrix such as chocolate.

The amount of microcapsules to be loaded into a single dosage unit will depend upon the [pharmaceutical being administered. For example, 200mg can

easily be formed into microcapsules and dispersed in a bite size unit dosage of matrix in a manner which will be substantially undiscernible to those eating the matrix. The maximum loading of microcapsules into the matrix will to a large extent be dependent upon the size of the microcapsules, the smaller the microcapsules, the larger the amount that can be loaded without being noticed when the matrix is ingested. For very tiny microcapsules, for example on the order of the size used in carbonless copy papers, it is conceivable that amounts as high as 50%, or even more, could be used without adversely affecting the consistency of the matrix. For example, if the dosage morsel of chocolate is very small, a unit dosage of medicament in very small microcapsules may be 500 mg in 1 gram of chocolate. Such a heavy loading, however, would not be preferred as substantial breakage of the microcapsules during chewing would be nearly unavoidable. However, the loading preferably should not exceed about 25–30% of the weight of the matrix and is most preferably less than 10%, depending on the average dose of the particular medicament being administered and the desired size of the dosage unit of matrix. A substantially bite-size dosage of matrix will generally be about 1–15g, depending on the density of the matrix.

When the matrix is chocolate, the microcapsules are preferably added to the chocolate in the process of its original production. For example, sweet chocolate and milk chocolate are made by mixing cocoa butter, sugar, chocolate liquor and, for milk chocolate, milk or milk solids. These are then refined to a fine particle size and then subjected to conching. Conching is a kneading process in which chocolate is slowly mixed, allowing moisture and volatile acids to escape while smoothing the remaining chocolate paste. Conching temperatures for sweet chocolate generally range from 55–85°C and from 45–55°C for milk chocolate. It is conventional to add flavors, emulsifiers, etc. during conching. Thus, the most appropriate time to add the microcapsules of the present invention in the chocolate production is also during conching. Of course, care must be taken that sufficient mixing occurs to obtain a substantially homogeneous distribution of microcapsules so that an accurate amount of medicament will be present in any given unit weight of chocolate.

Following conching, the product is standardized, tempered and molded in well known manners.

The microcapsules need not be added during conching, but may be added at any appropriate step during the production of chocolate, or may be added by taking completed chocolate, melting it, adding the microcapsules, mixing to homogeneity, and then again molding.

It should be understood that the manner of adding the microcapsules to the chocolate or other soft sweet matrix is not critical and any procedure can be used so long as a substantially homogeneous distributon of microcapsules is obtained.

Example 1

The microcapsules used in this example are those of the commerical drug "Contac", manufactured by Menley and James Laboratory (a Smith Kline Company). Each capsule contains 600 microcapsules, each of a diameter of about 0.5–0.8 mm. The microcapsules are prepared by pan-coating. Each capsule (i.e. 600 microcapsules) contains 75 mg phenylpropanolamine hydrochloride and 8 mg chlorpheniramine maleate.

The 600 microcapsules of one Contac capsule were embedded into chocolare by first heating a commercial chocolate square to melting (50°C) in an aluminum pan container, and then adding and mixing the microcapsules until a homogenous distribution of the capsules in the chocolate matrix was achieved, approximately 3 minutes. The chocolate was immediately cooled and molded into a unit of approximately 32mm × 20mm × 9mm.

When this chocolate was chewed, no taste of the drug was observed compared to a strong taste which was observed when the capsules were chewed without the chocolate. In addition, there was essentially no granular sensation upon chewing the chocolate pieces.

A sample of this chocolate was stored over one month at room temperature and then observed visually, and the stability of the drug was analyzed by mass spectroscopy analysis. After one month there was no change in the shape or number of the embedded microcapsules, and 100% of them could be recovered from the chocolate matrix. Mass spectrometic analysis of the embedded encapsulated drug showed it to be identical to a control sample (i.e., original microcapsules stored in commercial package). Thus, the introduction of the microcapsules into the chocolate matrix did not affect the stability or the chemical or physical state of the drugs in the microcapsules.

Example 2

The microcapsules used in this example were those of the commercial drug "Sudafed, S.A.", manufactured by Burroughs Wellcome Co. Each capsule contains about 300 microcapsules (diameter 0.6–0.9 mm). Each large capsule contains 120mg pseudoephedrine hydrochloride. These microcapsules were embedded in a single regular chocolate unit in the manner described in example 1. When the chocolate tablet was chewed and swallowed, no unpleasant taste of the

drug was detected.

Example 3

Microcapsules of aspirin coated with a hydrolized protein (gelatin) with an average diameter of 1.7μ to 2.0μ, each microcapsule comprising 99% aspirin, are prepared in the manner set forth in example 59 of U.S. patent 4,016,254. 40.4g of such microcapsules are added to 1kg of milk chocolate during the conching stage of the production thereof. After mixing to homogeneity, chocolate is standardized and tempered in a conventional manner, and then poured into molds to produce units of approximately 5g each. Each unit contains microcapsules which include 200mg of aspirin. The chocolate units may be chewed and swallowed with no unpleasant taste of aspirin being detectable.

Example 4

Microcapsules of aspirin coated with hydroxyphenylmethyl cellulose are prepared using the all-metal, conical Uni-Glatt 4"-Wurster apparatus. The average size of aspirin microcapsules was 80–180μ, in with each microcapsule comprising 93% aspirin and 7% coating.

A similar coating, under the same conditions, was carried out using cellulose acetylphthalate as coating material.

The above prepared microcapsules were embedded in chocolate (100mg encapsulated material per 1.5g chocolate) in the manner described in example 1. When the chocolate tablet was chewed and swallowed, no unpleasant taste of the drug was detected.

Example 5

Acetaminophen was encapsulated in 2.4% ethyl cellulose (Ethocel) and 1.05 hydroxypropylmethylcelluloe phthalate (HP 50). This coating was performed on the Aeromatic Strea-l fluidized bed apparatus. The average size of the obtained microcapsules was 80–120μ. The microcapsules were embedded in chocolate (100mg encapsulated material per 1.5g chocolate) in the matter described in Example 1. When the chocolate tablet was chewed and swallowed, no unpleasant taste of the drug was detected.

Example 6–13

The following drugs, each in encapsulated form with diameter of about 500–600μ, were embedded in 1.5g chocolate in the unit dosages specified. In each case no unpleasant taste of the drug was detected upon chewing and swallowing of the chocolate formulation.

Example No.	*Active Principle*	*Unit Dosage*
6	Theophylline	200 mg
7	Chlorpromazine hydrocloride	75 mg
8	Chlorpheniramine maleate	8 mg
9	Erythromycin	250 mg
10	Ferrous sulphate heptahydrate	167 mg
11	Nitroglycerin	2.5 mg
12	Papverine hydrochloride	150 mg
13	Niacin	250 mg

It will be obvious to those skilled in the art that various changes may be made without departing from the scope of the invention and the invention is not to be considered limited to what is described in the specification.

CLAIMS

1. A dosage form for the oral administration of a pharmaceutical active principle, comprising:

microencapsulated active principle embedded in a soft sweet palatable matrix.

2. A dosage form in accordance with claim 1, wherein a sufficient quantity of microencapsulated active principle is present in said matrix to provide a unit dose of said active principle in each bite-size unit of said matrix.

3. A dosage form in accordance with claim 1, wherein said soft, sweet, palatable matrix is sufficiently soft as to allow mastication thereof without the necessity of substantial chewing.

4. A dosage form in accordance with claim 1, wherein said matrix is selected from the group consisting of chocolate, fudge, marshmallow, peanut butter, carob or solid yogurt.

5. A dosage form in accordance with claim 1, wherein said matrix is chocolate.

6. A dosage form in accordance with claim 1, wherein said matrix is sweet chocolate or milk chocolate.

... claim 1, wherein said active principle is an anti-

sive agent, hypnotic, sedative, tranquilizer, alkaloid, diuretic, vasodilator, hormone or vitamin.

8. A dosage form in accordance with claim 1, wherein said microcapsules of active principle have a diameter of less than 1 mm.

9. A dosage form in accordance with claim 1, wherein said microcapsules of active principle have a diameter of about 10–100 microns.

10. A dosage form in accordance with claim 1, wherein the active principle is encapsulated in a material which prevents the active principle from coming into contact with said matrix throughout production and storage of the embedded matrix prior to use, is non-toxic and harmless, and permits release of the active principle in the stomach or gastro-intestinal tract after ingestion.

11. A method for oral administration of a pharmaceutical active principle without unpleasant or unpalatable taste or mouth feel, comprising:

orally administering to the patient a unit dose of a dosage form in accordance with claim 1.

12. A method in accordance with claim 11, wherein the patient is a child.

13. A method for the production of a dosage form for the oral administration of a pharmaceutical active principle, comprising:

microencapsulating the active principle; and

embedding the microencapsulated active principle in a soft, sweet, palatable matrix.

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